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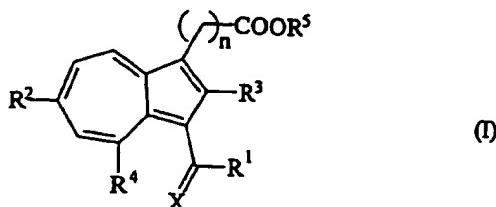
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(54) Abstract Title
Derivatives of Carboxyalkyl Azulenes and Azulene-1-Carboxylic Acid

(57) Compounds of formula (I):



wherein R¹ is a substituted or unsubstituted benzene ring or a heteroaromatic ring, R² and R³ are hydrogen or lower alkyl, R⁴ is hydrogen or lower alkoxy, R⁵ is hydrogen, lower alkyl or (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl, X is hydrogen, n is 0, 1 or 2 and pharmaceutically acceptable alkali addition salts thereof have activity as inhibitors of cyclooxygenase-2 and can therefore be used as analgesics and anti-inflammatory agents in the treatment of inflammation, pain, fever and arthritis; processes for preparing compounds of formula (I).

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AZULENE DERIVATIVES, METHOD OF MANUFACTURING THE SAME
AND PHARMACEUTICAL COMPOSITION CONTAINING THESE
COMPOUNDS.

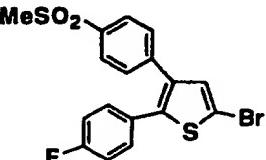
This invention relates to the azulene derivatives or their pharmaceutically acceptable alkali addition salts having antiinflammatory and analgesic activity. Furthermore, this invention relates to a manufacturing method of these azulene derivatives and a pharmaceutical composition containing these azulene derivatives.

Inflammation is the process of disorders which are characterized by redness, fever, swelling and pain. Arthritis is the frequently generated and the most severely inflammation disorder. Wound and infectious disease are also involved the inflammation and non-steroidal antiinflammatory drugs (NSAIDs) represented by aspirin and indomethacin have been used for treatment of these disorders. The therapeutic effect of NSAIDs is related to inhibition the formation of prostaglandins (PGs) via the cyclooxygenase (COX) pathway. On the other hand, the most common NSAIDs can produce side effects such as gastrointestinal irritation and suppression of renal function by the inhibition of COX enzyme, that may limit therapeutic potential.

Recently, it has shown that COX exists in two isozymes, termed COX-1 and COX-2. COX-1 is a constitutive enzyme, while COX-2 enzyme is induced specifically inflamed cells and tissues by inflammation. Accordingly, it indicates the possibility that a selective COX-2 inhibitor is NSAID having no side effects (Ensho to Meneki, 3 (1995). Nature, 367, 215, 1994. Drug News and Perspectives, 8, 501, 1994).

Currently, the following compounds have been proposed as selective or specific COX-2 inhibitors.

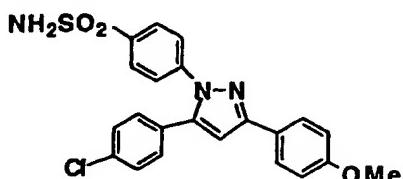
(1) The following compound has been proposed in Japanese Patent Publications No. 58-159489.



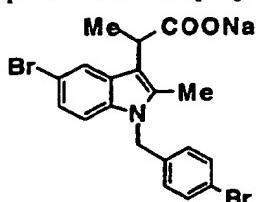
(2) The following compound has been proposed in Japanese Patent Publications No. 2-300122.



(3) The following compound has been proposed in WO-95-15318.

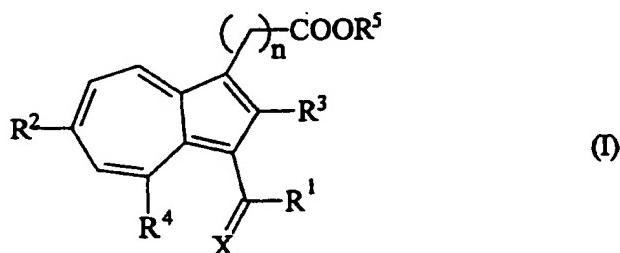


(4) The following compound has been proposed in US. Pat. No. 5510368.



The ratio between the therapeutic dose and the toxic dose of the most common NSAIDs is small. Therefore, the development of safe and effective NSAIDs is required. The object of the present invention is selective COX-2 inhibitor having excellent antiinflammatory, analgesic and antiarthritis activities without NSAIDs-associated side effects.

Accordingly, the present invention provides a compound which is an azulene derivative of formula (I):



wherein R¹ is a substituted or unsubstituted benzene ring or a heteroaromatic ring, R² is hydrogen or lower alkyl, R³ is hydrogen or lower alkyl, R⁴ is hydrogen or lower alkoxy, R⁵ is hydrogen, lower alkyl or (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl, X is hydrogen or oxygen and n is 0, 1 or 2; or a pharmaceutically acceptable alkali addition salt thereof.

When used to describe a functional group the term "lower" means straight or branched C₁-C₅.

Thus, for instance, lower alkyl is C₁-C₅ alkyl, preferably C₁-C₄ alkyl such as methyl, ethyl, i-propyl, n-propyl, t-butyl, s-butyl or n-butyl. Lower alkoxy is C₁-C₅ alkoxy, preferably C₁-C₄ alkoxy such as methoxy, ethoxy, i-propoxy, n-propoxy, t-butoxy, s-butoxy or n-butoxy.

In formula (I) R is a benzene or heteroaromatic ring which is unsubstituted or substituted by a substituent such as lower alkyl, halogenated lower alkyl, lower alkoxy or halogen. This substituent is in turn optionally substituted by one or two substituents selected from those defined above. In the case of a di-substituted ring, the two substituents on the phenyl ring are the same or different. The heteroaromatic ring is preferably a furan or thiophene ring.

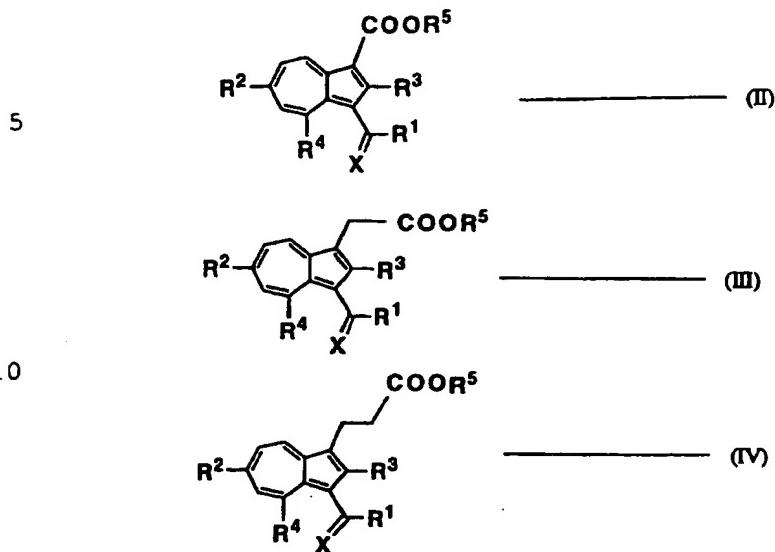
R² is hydrogen or lower alkyl. R³ is hydrogen or lower alkyl. R⁴ is hydrogen or lower alkoxy. R⁵ is hydrogen, lower alkoxy or (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl. X is hydrogen or an oxygen atom and n is 0, 1 or 2.

The term "pharmaceutically acceptable salts" means that the salts maintain biological efficacy and property of the compounds of this invention.

Pharmaceutically acceptable salts are often preferred in the biological field. Alkali addition salts may be prepared from an inorganic base or from an organic base. The base addition salts may be prepared from an inorganic base or from an organic base. The base addition salts may be prepared from inorganic bases such as lithium hydroxide, sodium hydroxide, potassium hydroxide, calcium hydroxide, magnesium hydroxide or ammonia. The salts prepared from organic bases may be formed from the primary, secondary or tertiary amines, natural occurring substituted amines and cyclic amines such as isopropylamine, triethylamine, diethylamine, ethanolamine, pyridine, lysine, arginine or piperidine.

In a preferred aspect of the invention R¹ is a benzene, furan or thiophene ring which is unsubstituted or substituted by one or two substituents selected from methyl, trifluoromethyl, methoxy, chlorine and bromine, R² is hydrogen or isopropyl, R³ is hydrogen, methyl, ethyl or isopropyl, R⁴ is hydrogen or methoxy, R⁵ is hydrogen, ethyl or (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl, X is

hydrogen or oxygen and n is 1 or 2. Accordingly, preferred structures of compounds of the invention are represented by the formulae (II) to (IV):



15 wherein R¹ to R⁵ are as defined above.

Some compounds of formula (I) are as follows.

- (1) 3-Benzoyl-2-methylazulene-1-carboxylic acid (compound 1)
- (2) 3-Benzoyl-6-isopropyl-2-methylazulene-1-carboxylic acid (compound 2)
- (3) 3-(2-Chlorobenzoyl)-2-methylazulene-1-carboxylic acid (compound 3)
- (4) 3-(3-Chlorobenzoyl)-2-methylazulene-1-carboxylic acid (compound 4)
- (5) 3-(4-Chlorobenzoyl)-2-methylazulene-1-carboxylic acid (compound 5)
- (6) 3-(3-Chlorobenzoyl)-6-isopropyl-2-methylazulene-1-carboxylic acid (compound 6)
- (7) 3-(3-Bromobenzoyl)-2-methylazulene-1-carboxylic acid (compound 7)
- (8) 3-(4-Bromobenzoyl)-2-methylazulene-1-carboxylic acid (compound 8)
- (9) 3-(4-Bromobenzoyl)-6-isopropyl-2-methylazulene-1-carboxylic acid (compound 9)
- (10) 3-(3-Methylbenzoyl)-2-methylazulene-1-carboxylic acid (compound 10)
- (11) 3-(4-Methylbenzoyl)-2-methylazulene-1-carboxylic acid (compound 11)
- (12) 3-(4-Methoxybenzoyl)-2-methylazulene-1-carboxylic acid (compound 12)
- (13) 2-Methyl-3-(4-trifluoromethylbenzoyl)azulene-1-carboxylic acid (compound 13)
- (14) 3-(3-Chloro-4-methoxybenzoyl)-2-methylazulene-1-carboxylic acid (compound 14)
- (15) 3-(3,5-Dichlorobenzoyl)-2-methylazulene-1-carboxylic acid (compound 15)
- (16) 3-(2-Furyl)-2-methylazulene-1-carboxylic acid (compound 16)
- (17) 2-Methyl-3-(2-thenoyl)azulene-1-carboxylic acid (compound 17)
- (18) (3-Benzoyl-2-methylazulene-1-yl)acetic acid (compound 18)
- (19) (3-Benzoyl-6-isopropyl-2-methylazulene-1-yl)acetic acid (compound 19)
- (20) [3-(2-Chlorobenzoyl)-2-methylazulene-1-yl]acetic acid (compound 20)

- (21) [3-(3-Chlorobenzoyl)-2-methylazulene-1-yl]acetic acid (compound 21)
- (22) [3-(4-Chlorobenzoyl)-2-methylazulene-1-yl]acetic acid (compound 22)
- (23) [3-(4-Chlorobenzoyl)-6-isopropyl-2-methylazulene-1-yl]acetic acid (compound 23)
- (24) [3-(3-Bromobenzoyl)-2-methylazulene-1-yl]acetic acid (compound 24)
- (25) [3-(4-Bromobenzoyl)-2-methylazulene-1-yl]acetic acid (compound 25)
- (26) [3-(4-Bromobenzoyl)-6-isopropyl-2-methylazulene-1-yl]acetic acid (compound 26)
- (27) [3-(3-Methylbenzoyl)-2-methylazulene-1-yl]acetic acid (compound 27)
- (28) [3-(4-Methylbenzoyl)-2-methylazulene-1-yl]acetic acid (compound 28)
- (29) [3-(4-Methoxybenzoyl)-2-methylazulene-1-yl]acetic acid (compound 29)
- (30) [2-Methyl-3-(4-trifluoromethylbenzoyl)azulene-1-yl]acetic acid (compound 30)
- (31) [3-(3-Chloro-4-methoxybenzoyl)-2-methylazulene-1-yl]acetic acid (compound 31)
- (32) [3-(3,5-Dichlorobenzoyl)-2-methylazulene-1-yl]acetic acid (compound 32)
- (33) [3-(2-Furoyl)-2-methylazulene-1-yl]acetic acid (compound 33)
- (34) [2-Methyl-3-(2-thenoyl)azulene-1-yl]acetic acid (compound 34)
- (35) (3-Benzyl-2-methylazulene-1-yl)acetic acid (compound 35)
- (36) (3-Benzyl-6-isopropyl-2-methylazulene-1-yl)acetic acid (compound 36)
- (37) [3-(4-Chlorobenzyl)-2-methylazulene-1-yl]acetic acid (compound 37)
- (38) 3-(3-Benzoyl-2-methylazulene-1-yl)propionic acid (compound 38)
- (39) 3-(3-Benzoyl-6-isopropyl-2-methylazulene-1-yl)propionic acid (compound 39)
- (40) 3-[3-(2-Chlorobenzoyl)-2-methylazulene-1-yl]propionic acid (compound 40)
- (41) 3-[3-(3-Chlorobenzoyl)-2-methylazulene-1-yl]propionic acid (compound 41)
- (42) 3-[3-(4-Chlorobenzoyl)-2-methylazulene-1-yl]propionic acid (compound 42)
- (43) 3-[3-(4-Chlorobenzoyl)-6-isopropyl-2-methylazulene-1-yl]propionic acid (compound 43)
- (44) 3-[3-(2-Bromobenzoyl)-2-methylazulene-1-yl]propionic acid (compound 44)
- (45) 3-[3-(3-Bromobenzoyl)-2-methylazulene-1-yl]propionic acid (compound 45)
- (46) 3-[3-(4-Bromobenzoyl)-2-methylazulene-1-yl]propionic acid (compound 46)
- (47) 3-[3-(4-Bromobenzoyl)-6-isopropyl-2-methylazulene-1-yl]propionic acid (compound 47)
- (48) 3-[3-(3-Methylbenzoyl)-2-methylazulene-1-yl]propionic acid (compound 48)
- (49) 3-[3-(4-Methylbenzoyl)-2-methylazulene-1-yl]propionic acid (compound 49)
- (50) 3-[3-(4-Methoxybenzoyl)-2-methylazulene-1-yl]propionic acid (compound 50)
- (51) 3-[2-Methyl-3-(4-trifluoromethylbenzoyl)azulene-1-yl]propionic acid (compound 51)
- (52) 3-[3-(3-Chloro-4-methoxybenzoyl)-2-methylazulene-1-yl]propionic acid (compound 52)
- (53) 3-[3-(3,5-Dichlorobenzoyl)-2-methylazulene-1-yl]propionic acid (compound 53)
- (54) 3-[3-(2-Furoyl)-2-methylazulene-1-yl]propionic acid (compound 54)
- (55) 3-[2-Methyl-3-(2-thenoyl)azulene-1-yl]propionic acid (compound 55)
- (56) 3-(3-Benzyl-2-methylazulene-1-yl)propionic acid (compound 56)

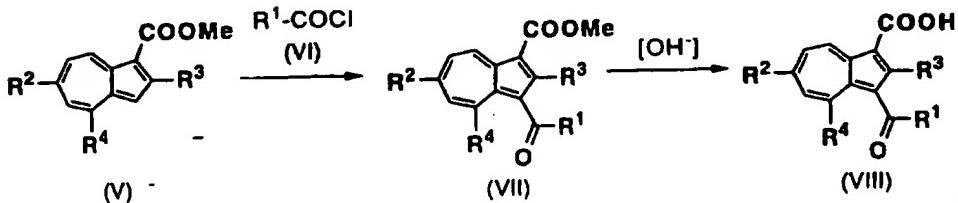
- (57) 3-[3-(4-Chlorobenzyl)-2-methylazulene-1-yl]propionic acid (compound 57)
 (58) 3-Benzoylazulene-1-carboxylic acid (compound 58)
 (59) 3-Benzylazulene-1-carboxylic acid (compound 59)
 (60) 3-Benzoyl-2-ethylazulene-1-carboxylic acid (compound 60)
 (61) (3-Benzoyl-2-ethylazulene-1-yl)acetic acid (compound 61)
 (62) 3-Benzoyl-2-isopropylazulene-1-carboxylic acid (compound 62)
 (63) (3-Benzoyl-2-isopropylazulene-1-yl)acetic acid (compound 63)
 (64) 3-Benzoyl-4-methoxy-2-methylazulene-1-carboxylic acid (compound 64)
 (65) (3-Benzoyl-4-methoxy-2-methylazulene-1-yl)acetic acid (compound 65)
 (66) Ethyl (3-benzoyl-2-methylazulene-1-yl)acetate (compound 66)
 (67) Ethyl [3-(2-chlorobenzoyl)-2-methylazulene-1-yl]acetate (compound 67)
 (68) Ethyl [3-(4-methylbenzoyl)-2-methylazulene-1-yl]acetate (compound 68)
 (69) Ethyl [3-(4-bromobenzoyl)-2-methylazulene-1-yl]acetate (compound 69)
 (70) Ethyl [2-methyl-3-(2-thenoyl)azulene-1-yl]acetate (compound 70)
 (71) (5-Methyl-2-oxo-1,3-dioxol-4-yl)methyl(3-benzoyl-2-methylazulene-1-yl)acetate (compound 71)
 (72) (5-Methyl-2-oxo-1,3-dioxol-4-yl)methyl [3-(2-chlorobenzoyl)-2-methylazulene-1-yl]acetate
 (compound 72)
 (73) (5-Methyl-2-oxo-1,3-dioxol-4-yl)methyl [3-(4-methylbenzoyl)-2-methylazulene-1-yl]acetate
 (compound 73)
 (74) (5-Methyl-2-oxo-1,3-dioxol-4-yl)methyl [3-(4-bromobenzoyl)-2-methylazulene-1-yl]acetate
 (compound 74)
 (75) (5-Methyl-2-oxo-1,3-dioxol-4-yl)methyl [2-methyl-3-(2-thenoyl)azulene-1-yl]acetate
 (compound 75)

The above mentioned compounds numbered from (1) to (75) will be referred to herein after, as compound 1, compound 2, --, compound 75, respectively.

The compounds of the present invention can be synthesized by several methods. The represented synthetic methods of these compounds are shown in the following schemes.

Scheme 1

The synthetic method of 3-benzoyl-2-methylazulene-1-carboxylic acid derivatives.



R¹, R², R³ and R⁴ in formulae (V), (VII) and (VIII) are defined as aforesaid.

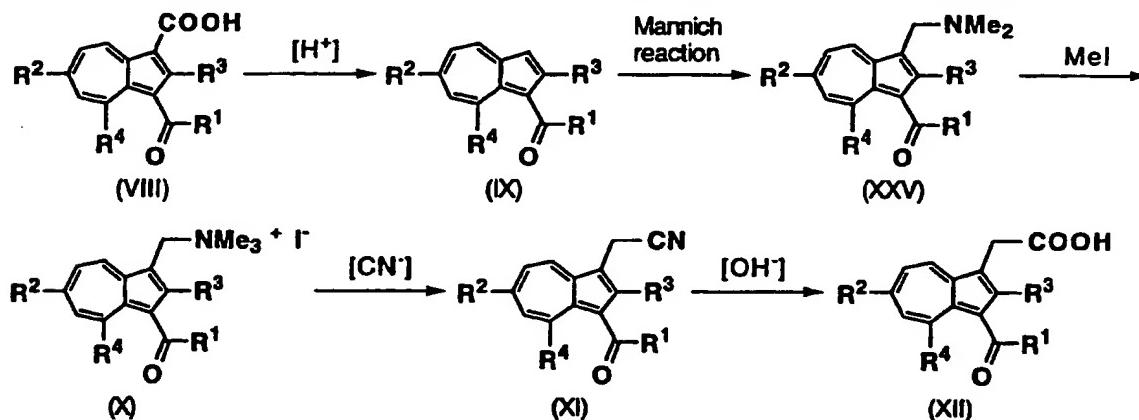
Methyl 2-alkylazulene-1-carboxylate (V), a starting material in this sequence, is obtained by the reported method (Tetrahedron Lett., 4275 (1971)).

5 Process 1 is the method for obtain the compound of general formula (VII) by the Friedel-Crafts reaction of compound of general formula (V), which is synthesized in the first synthetic method. The acid chlorides of general formula (VI) are suitable acylating agents for Friedel-Crafts reaction and this reaction is carried out in the presence of Lewis acids such as aluminium chloride, titanium tetrachloride, tin tetrachloride or boron trifluoride in reaction-inert organic solvents such as dichloromethane, 1, 1, 2, 2-tertachloroethane carbondisulfide or nitrobenzene under heating conditions.

10 Process 2 is the method for obtain carboxylic acid of general formula (VIII) by the hydrolysis of compound of general formula (VII) under basic conditions. The aqueous solutions of sodium hydroxide, potassium hydroxide and lithium hydroxide can be employed for the hydrolysis and this reaction is carried out in reaction-inert organic solvents such as methanol, ethanol, tetrahydrofuran or dioxane under heating conditions.

Scheme 2

The synthetic method of (3-benzoyl-2-methylazulene-1-yl)acetic acid derivatives (Part 1)



R¹, R², R³ and R⁴ in formulae (VIII), (IX), (XXV), (X), (XI) and (XII) are defined as aforesaid. Step 1 is the production of a compound of formula (IX) by the demethoxycarbonylation of a compound of formula (VIII). Sulfuric acid, *p*-toluenesulfonic acid, trifluoroacetic acid, phosphoric acid and malic acid are suitable acids for the demethoxycarbonylation of a compound of formula (X). The reaction is carried out in reaction-inert organic solvents such as benzene under heating conditions.

Step 2 is the production of an amine of formula (XXV) by the Mannich reaction of a compound of general formula (IX).

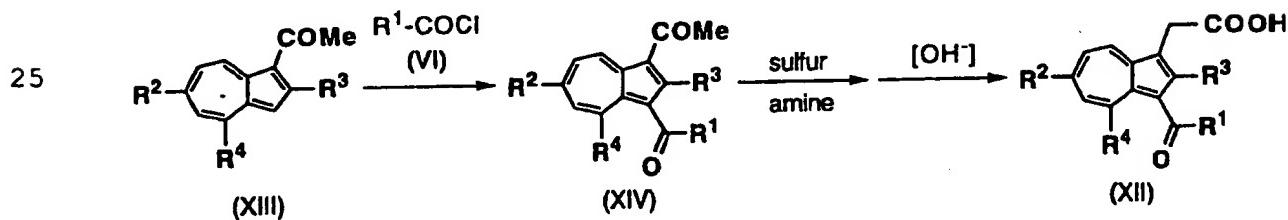
Step 3 is the production of a quaternary ammonium salt of formula (X) by the reaction of compound of general formula (XXV) with methyl iodide. The reaction is conducted in reaction-inert organic solvents such as methanol, ethanol, acetone, dichloromethane, chloroform, benzene or toluene under heating conditions.

Step 4 is the production of a nitrile of formula (XI) by the cyanation of a compound of formula (X). Sodium cyanide and potassium cyanide are suitable for the cyanation. Preferred reaction solvents for use in this reaction include methanol, ethanol, acetone, dichloromethane, chloroform, benzene, toluene, *N,N*-dimethylformamide and dimethylsulfoxide and the reaction is carried out under heating conditions.

Step 5 is the production of a carboxylic acid of formula (XIII) by the hydrolysis of a compound of formula (XI). The compound of formula (XI) can be hydrolyzed under acidic or basic conditions. Aqueous solutions of hydrogen chloride, sulfonic acid, sodium hydroxide, potassium hydroxide and lithium hydroxide are suitable acids and bases for this hydrolysis and the reaction is carried out in reaction-inert organic solvents such as methanol, ethanol, tetrahydrofuran and dioxane under heating conditions.

Scheme 3

The synthetic method of (3-benzoyl-2-methylazulene-1-yl)acetic acid (Part 2).



R¹, R², R³ and R⁴ in formulae (XIII), (XIV) and (XII) are defined as aforesaid. 1-Acetyl-2-alkylazulene (XIII), a starting material in this sequence, is obtained by the reported method (Tetrahedron Lett., 4275 (1971)).

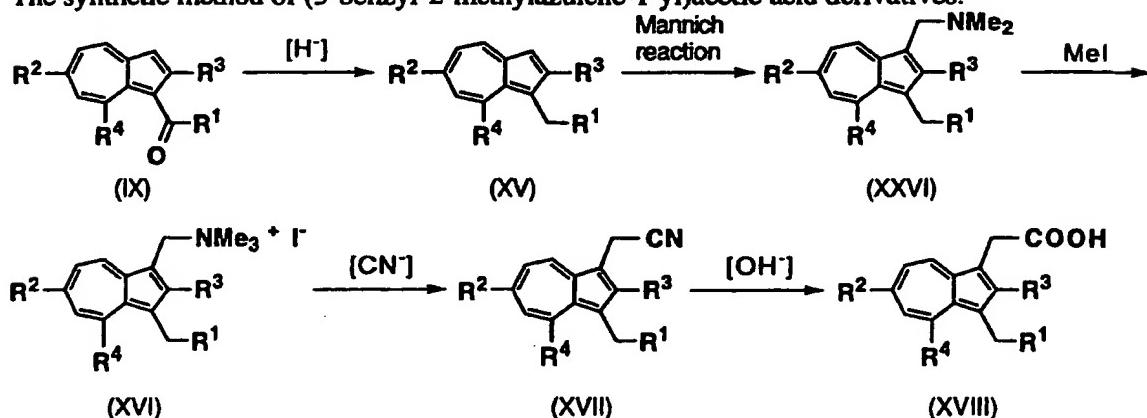
Step 1 is the production of a compound of formula (XIV) by the Friedel-Crafts reaction of a compound of formula (XIII), which is synthesized in the first synthetic method.

The acid chlorides of general formula (VI) are suitable acylating agents for Friedel-Crafts reaction and this reaction is carried out in the presence of Lewis acids such as aluminium chloride, titanium tetrachloride, tin tetrachloride or boron trifluoride in reaction-inert organic solvents such as dichloromethane, 1,1,2,2-tetrachloroethane carbondisulfide or nitrobenzene under heating conditions.

Step 2 is the production of a carboxylic acid of formula (XII) by the Willgerodt-Kindler reaction of a compound of formula (XIV) and hydrolysis of the resulting thioamide. The Wilgerodt-Kindler reaction is carried out using sulfur in secondary amines such as dimethylamine, morpholine or piperidine and/or in reaction-inert organic solvents such as pyridine or dioxane under heating conditions. The thioamide derivatives obtained by the Wilgerodt-Kindler reaction can be hydrolyzed under acidic or basic conditions. Aqueous solutions of hydrogen chloride, sulfonic acid, sodium hydroxide, potassium hydroxide and lithium hydroxide are suitable acids and bases for this hydrolysis and the reaction is carried out in reaction-inert organic solvents such as methanol, ethanol, tetrahydrofuran and dioxane under heating conditions.

Scheme 4

The synthetic method of (3-benzyl-2-methylazulene-1-yl)acetic acid derivatives.



30 R^1 , R^2 , R^3 and R^4 in this reaction scheme are defined as aforesaid.

Step 1 is the production of a compound of formula (XV) by the reduction of

the carbonyl group in a compound of formula (IX). The reduction can be conducted using a mixed reducing agent prepared from reducing agents such as boran, triethylsilane, sodium borohydride, sodium cyanoborohydride or lithium aluminium hydride and Lewis acids such as aluminium chloride, titanium tetrachloride, tin tetrachloride or boron trifluoride. The reaction is carried out in reaction-inert organic solvents such as ether or tetrahydrofuran under heating conditions.

Step 2 is the production of an amine of formula (XXVI) by the Mannich reaction of a compound of formula (XV).

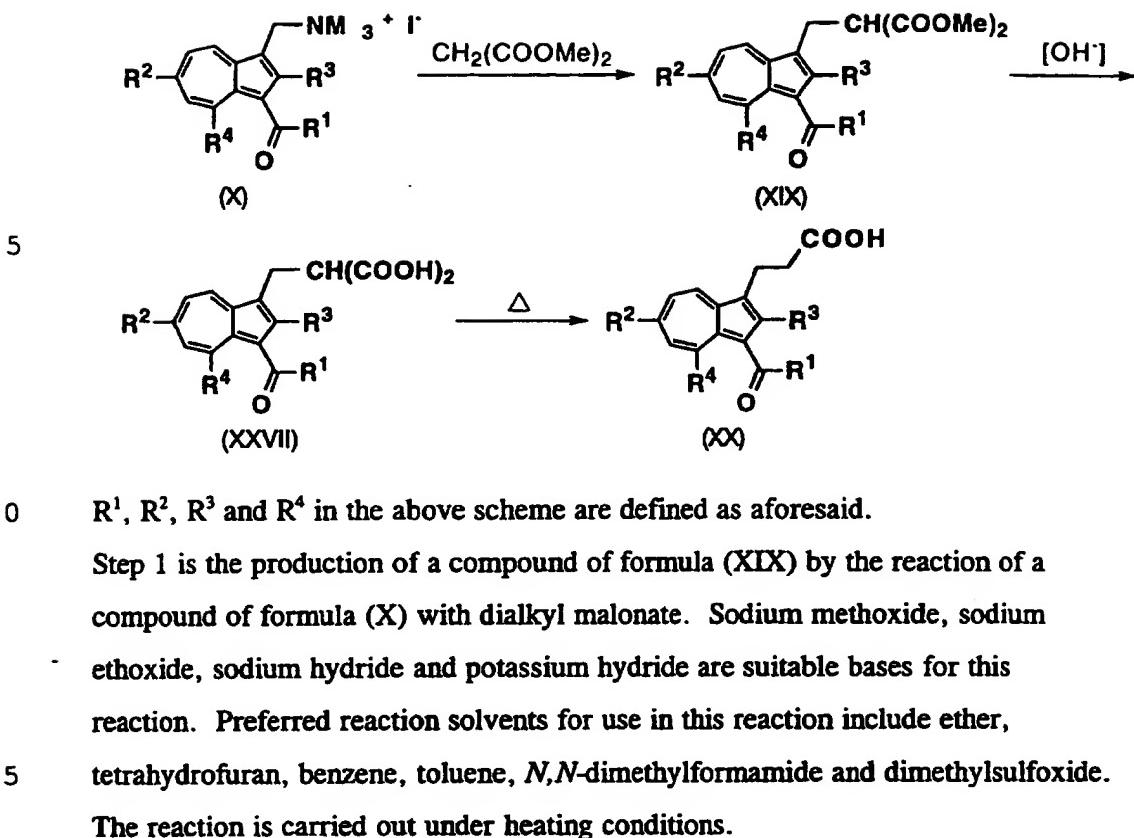
Step 3 is the production of a quaternary ammonium salt of formula (XVI) by the reaction of a compound of formula (XXVI) with methyl iodide. The reaction is conducted in reaction-inert organic solvents such as methanol, ethanol, acetone, dichloromethane, chloroform, benzene or toluene under heating conditions.

Step 4 is the production of a nitrile of formula (XVII) by the cyanation of a compound of formula (X). Sodium cyanide and potassium cyanide are suitable cyanides for the cyanation of a compound of formula (X). Preferred reaction solvents involve methanol, ethanol, acetone, dichloromethane, chloroform, benzene, toluene, *N,N*-dimethylformamide and dimethylsulfoxide and the reaction is carried out under heating conditions.

Step 5 is the production of a carboxylic acid of formula (XVIII) by the hydrolysis of a compound of formula (XVII). The compound of formula (XVII) can be hydrolyzed under acidic or basic conditions. Aqueous solutions of hydrogen chloride, sulfonic acid, sodium hydroxide, potassium hydroxide and lithium hydroxide are suitable acids and bases for this hydrolysis and the reaction is carried out in reaction-inert organic solvents such as methanol, ethanol, tetrahydrofuran and dioxane under heating conditions.

Scheme 5

The synthetic method of 3-(3-benzoyl-2-methylazulene-1-yl)propionic acid derivatives.



10 $\text{R}^1, \text{R}^2, \text{R}^3$ and R^4 in the above scheme are defined as aforesaid.

Step 1 is the production of a compound of formula (XIX) by the reaction of a compound of formula (X) with dialkyl malonate. Sodium methoxide, sodium ethoxide, sodium hydride and potassium hydride are suitable bases for this reaction. Preferred reaction solvents for use in this reaction include ether, tetrahydrofuran, benzene, toluene, *N,N*-dimethylformamide and dimethylsulfoxide.

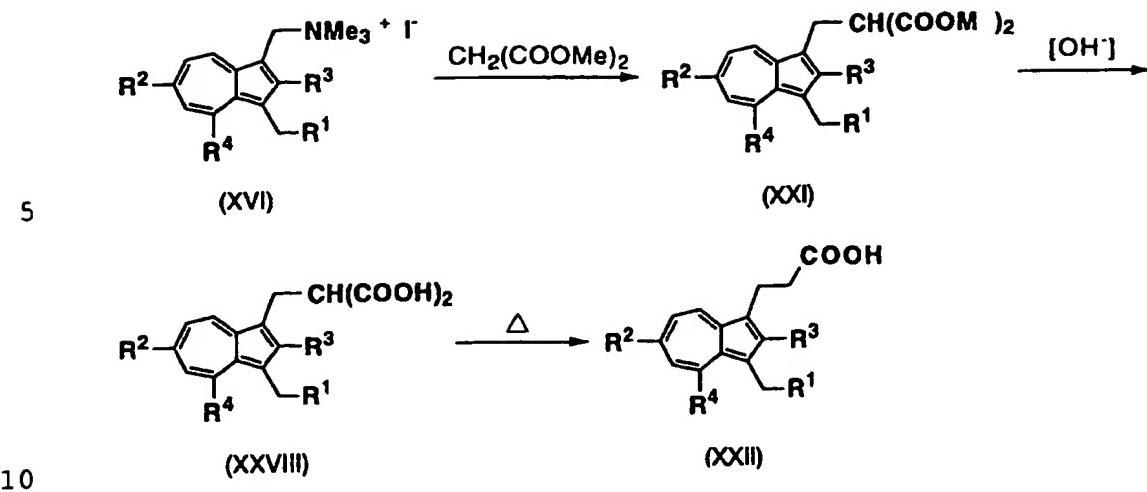
The reaction is carried out under heating conditions.

Step 2 is the production of a dicarboxylic acid of formula (XXVII) by the hydrolysis of a compound of formula (XIX) under basic conditions. Aqueous solutions of sodium hydroxide, potassium hydroxide and lithium hydroxide can be employed for the hydrolysis and this reaction is carried out in reaction-inert organic solvents such as methanol, ethanol, tetrahydrofuran or dioxane. Preferred reaction temperatures are in the range of from room temperature up to the reflux temperature of the reaction mixture.

Step 3 is the production of a compound of formula (XX) by the decarbonylation of a compound of formula (XXVII). The reaction is carried out in reaction-inert organic solvents such as benzene, toluene or dioxane under heating conditions.

Scheme 6

30 The synthetic method of 3-(3-benzyl-2-methylazulene-1-yl) propionic acid derivatives.



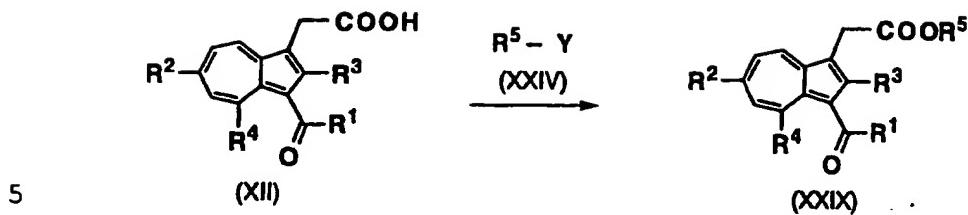
R¹, R², R³ and R⁴ in the above scheme are defined as aforesaid.

Step 1 is the production of a compound of formula (XXI) by the reaction of a compound of formula (XVI) with dialkyl malonate. Sodium methoxide, sodium ethoxide, sodium hydride and potassium hydride are suitable bases for this reaction. Preferred reaction solvents for use in this reaction include ether, tetrahydrofuran, benzene, toluene, *N,N*-dimethylformamide and dimethylsulfoxide. The reaction is carried out under heating conditions.

Step 2 is the production of a dicarboxylic acid for formula (XXVIII) by the hydrolysis to a compound of formula (XXI) under basic conditions. Aqueous solutions of sodium hydroxide, potassium hydroxide and lithium hydroxide can be employed for the hydrolysis and this reaction is carried out in reaction-inert organic solvents such as methanol, ethanol, tetrahydrofuran or dioxane. Preferred reaction temperatures are in the range of from room temperature up to the reflux temperature of the reaction mixture.

Step 3 is the production of a compound of formula (XXII) by the decarbonylation of a compound of formula (XXVIII). The reaction is carried out in reaction-inert organic solvents such as benzene, toluene or dioxane under heating conditions.

Scheme 7



R¹, R², R³, R⁴, R⁵ and Y in the above scheme are defined as aforesaid. This process leads to the ester of formula (XXIX) by the reaction of a compound of formula (XII) with an alkyl halide of formula (XXIV). This reaction is carried out
10 in the presence of a base in reaction-inert organic solvents such as *N,N*-dimethylformamide, *N,N*-dimethylacetamide, hexamethylphosphoric triamide, dimethylsulfoxide, acetone,

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tetrahydrofuran, dioxane or chloroform at room temperature or under heating conditions.

Sodium hydrogencarbonate, sodium carbonate, potassium carbonate, triethylamine and pyridine are suitable bases for this reaction.

The reaction products are isolated and are purified as free acids or pharmaceutically acceptable alkali-addition salts. The pharmaceutically acceptable alkali-addition salts are prepared by conventional methods. The reaction products are purified using extraction, concentration, evaporation, crystallization, filtration, recrystallization or chromatography. be combined with various pharmaceutically acceptable inert carriers or diluents (soluble starch, lactose, sucrose, calcium carbonate, calcium phosphate), binders (soluble starch, acacia, carboxymethylcellulose, hydroxymethylcellulose, crystalline cellulose, alginic acid, gelatin, polyvinylpyridone), lubricants (stearic acid, magnesium stearate, calcium stearate, tal), disintegrants (carboxymethylcellulose, talc) or pharmaceutical solvents (saline). They can be administered orally or parenterally in the form of powders, granula subtilaes, tablets, capsules, external applications and injections.

In general, these compounds of the present invention and their pharmaceutically acceptable alkali-addition salts are administered in dosage ranging from 50 mg up to 5 g per day, although variations will necessarily occur depending upon the weight and conditions of the recipient. Preferably, 100 mg to 500 mg per day given in divided dosage 1 to 3 times a day. The examples of typical dosage are 10 mg, 50 mg, 100 mg, 200 mg, 500 mg and 1g, although they dose not be limited.

The improtant property of present invention is that inflammation and pain in a mammal are treated by the administration of the effective dose of compounds of general formula (I) or their pharmaceutically acceptable salts as antiinflammatory agents. The compound of general formula (I) is useful antiinflammatory agents without NSAIDs-associated gastorintestinal irritation. Similarly, these compounds are expected to have no renal toxicity.

As above, the compound of this invention is NSAIDs without gastoric toxicity. NSAIDs prevent the production of PGs by inhibiting COX-1 and COX-2 which involve cyclooxygenation of arachidonic acid to PGG₂ and peroxidase reaction of PGG₂ to PGH₂. COX-1 enzyme is expressed in normal tissues such as stomach and renal, while COX-2 isoform is found to be located primary in inflamed cells and tissues. It seems that selective or specific COX-2 inhibitors shows the antiinflammatory and analgesic activities, which are the desired therapeutic effects of NSAIDs, without side effect such as gastointestinal irritation and suppression of renal function. Further more hand, compounds in this invention are expected to have a usefulness for cancer therapy. Especially, it is thought that these compounds, as like other inhibitors of PG biosynthesis, inhibits the metastasis of benign or partially transformed colon polyp (Acta Histochemica Suppementband, 29, 195, 1990).

Furthermore, COX-2 inhibitors reduce the risks of colorectal carcinoma, and it is reported that COX-2 is highly expressed in apoptosis. From these findings, it is expected to use of COX-2 inhibitors for cancer and apoptosis therapy (Cell, 83, 345, 1995).

Pharmacological experiment are as follows.

Inhibitory activity of compounds on COX-1 and COX-2.

Inhibitory activity of compounds on COX-1 and COX-2 were assayed according to the method of Needleman (J. Biol. Chem., 254, 9772, 1979). One unit of COX-1 enzyme from sheep seminal vesicle or COX-2 enzyme from sheep placenta, suspended with 100 mM Tris-HCl buffer (pH 8.0, 500 μ l) containing 1 μ M hematin as co-factor, was incubated with compound and 1 mM arachidonic acid at 37 °C for 10 min. The reaction was stopped with 2.5 mM indomethacin, and amounts of PGE₂ in the reaction mixture was assayed using PGE₂ EIA system. IC₅₀ (the concentrations which inhibited PGE₂ production by 50 %) were calculated and shown in Table 1.

[Table 1]

Compounds	COX-1 IC ₅₀ (μ M)	COX-2 IC ₅₀ (μ M)
18	3.1	0.13
19	10.0	2.2
20	2.5	0.44
22	0.012	0.16
25	0.033	0.93
26	0.058	0.93
28	0.048	0.10
29	0.051	0.099
34	>10.0	3.0
37	1.7	1.6

Estimation of antiinflammatory action.

Carageenan-induced rat paw edema (Proc. Soc. Exp. Biol. N. Y., 544, 114 (1962))

Male Sprague-Dawley rats (150-200 g) were fasted for 18 hr before use and were given orally either a vehicle (0.5% methylcellulose in distilled water, 5 ml/kg) or a compound. Thirty minutes later, 100 μ l of 1% λ -carrageenan solution was injected subcutaneously into the right hind paw and paw volume was measured using a plethysmometer (Ugo-Basile). Swelling was evaluated compared with a paw volume before carrageenan injection.

Oral administration of compound 18 at dose of 2.8 mg/kg inhibited the carageenan-induced paw edema by 40 %.

The invention will be further described in the Examples which follow.

Example 1: 3-Benzoyl-2-methylazulene-1-carboxylic acid (compound 1)

(a) Methyl 3-benzoyl-2-methylazulene-1-carboxylate

To a solution of methyl 2-methylazulene-1-carboxylate (4.0 g) in CH_2Cl_2 (50.0 ml) was added AlCl_3 (5.3 g) at 0 °C, and the reaction mixture was stirred for 20 min at same temperature. Then, benzoyl chloride (4.6 g) was added at same temperature, and the reaction mixture was heated under reflux for 1 hr. The mixture was poured into ice-water, and extracted with Et_2O . The combined Et_2O extracts were washed with water and brine, dried over Na_2SO_4 , and concentrated. The crude product was purified by SiO_2 column chromatography ($\text{AcOEt}/n\text{-hexane}$, 1:5) to give the title compound (5.8 g) as violet crystals; mp 104-106 °C;

$^1\text{H NMR}$ (CDCl_3): δ = 2.63 (3H, s), 4.00 (3H, s), 7.45 (2H, t), 7.51 (1H, t), 7.58 (1H, t), 7.67 (1H, t), 7.77 (2H, d), 7.79 (1H, t), 8.59 (1H, d), 9.63 (1H, d).

(b) 3-Benzoyl-2-methylazulene-1-carboxylic acid (compound 1)

To a solution of methyl 3-benzoyl-2-methylazulene-1-carboxylate (5.8 g) in MeOH (50.0 ml) was added 10% aqueous NaOH (25.0 ml), and the reaction mixture was heated under reflux for 2 hr. After removal of solvent, the aqueous layer was washed with Et_2O . The aqueous solution was adjusted to pH 2 with 10% aqueous HCl . Then the crystals was collected by filtration, washed with water, and recrystallized from MeOH to give the title compound (4.86 g) as violet crystals; mp 190-192 °C;

$^1\text{H NMR}$ (DMSO-d_6): δ = 2.25 (3H, s), 7.53 (2H, t), 7.63-7.70 (4H, m), 7.83 (1H, t), 8.00 (1H, t), 8.47 (1H, d), 9.63 (1H, d), 12.77 (1H, s).

Example 2: (3-Benzoyl-2-methylazulene-1-yl)acetic acid (Compound 18)

(a) 1-Benzoyl-2-methylazulene

To a suspension of 3-benzoyl-2-methylazulene-1-carboxylic acid (0.50 g) in benzene (15.0 ml) was added *p*-toluenesulfonic acid monohydrate (0.01 g), and the reaction mixture was heated under reflux for 1 hr. The mixture was diluted with Et_2O , washed with saturated aqueous NaHCO_3 and brine, dried over Na_2SO_4 , and concentrated. The crude product was purified by SiO_2 column chromatography ($\text{EtOAc}/n\text{-hexane}$, 1:5) to give the title compound (0.40 g) as violet oil;

$^1\text{H NMR}$ (CDCl_3): δ = 2.45 (3H, s), 7.19 (1H, s), 7.3 (1H, t), 7.38 (1H, t), 7.43-7.53 (2H, m), 7.56 (1H, t), 7.64 (1H, t), 7.47-7.76 (2H, m), 8.31 (1H, d), 8.57 (1H, d).

(b) 1-(3-Benzoyl-2-methyl)methylazulenetrtrimethylammonium iodide

A mixture of paraformaldehyde (0.17 g), *N,N,N',N'*-tetramethyldiaminomethane (0.92 g) and acetic acid (17.0 ml) was heated and stirred at 80 °C for 20 min. Then a solution of 1-benzoyl-2-

methylazulene (2.0 g) in CH_2Cl_2 (34.0 ml) was added at 0°C, and the reaction mixture was stirred at room temperature for 1 hr. The reaction mixture was adjusted to pH 10 with 10% aqueous NaOH, and extracted with CH_2Cl_2 . The combined CH_2Cl_2 extracts were washed with water and brine, dried over Na_2SO_4 , and concentrated. Methyl iodide (10.0 ml) was added to the solution of the crude product in EtOH (20.0 ml), and the reaction mixture was stirred at room temperature for 2 hr. Then the crystals were collected by filtration to give the title compound (3.32 g) as violet crystals; mp 132-133 °C;

^1H NMR (CDCl_3): d = 2.64 (3H, s), 3.50 (9H, s), 5.18 (1H, bs), 5.89 (1H, d), 7.44 (1H, t), 7.46 (1H, t), 7.59 (1H, t), 7.71 (2H, d), 7.80 (1H, t), 7.84 (1H, t), 8.47 (1H, d), 9.74 (1H, d).

(c) 3-Benzoyl-2-methyl-1-cyanomethylazulene

To a suspension of 1-(3-benzoyl-2-methyl)methylazulenetrtrimethylammonium iodide (1.0 g) in EtOH (20.0 ml) was added KCN (0.25 g), and the reaction mixture was heated under reflux for 2 hr. The reaction mixture was poured into ice-water, and extracted with Et_2O . The combined Et_2O extracts were washed with water and brine, dried over Na_2SO_4 , and concentrated. The crude product was purified by SiO_2 column chromatography ($\text{Et}_2\text{O}/n$ -hexane, 3:2) to give the title compound (0.31 g) as violet crystals; mp 82-83 °C;

^1H NMR (CDCl_3): d = 2.50 (3H, s), 4.08 (2H, s), 7.37 (1H, t), 7.45-7.52 (3H, m), 7.59 (1H, t), 7.71-7.77 (3H, m), 8.35 (1H, d), 8.55 (1H, d).

(d) (3-Benzoyl-2-methylazulene-1-yl)acetic acid (compound 18)

To a suspension of 3-benzoyl-2-methyl-1-cyanomethylazulene (0.29 g) in EtOH (10.0 ml) was added 20% aqueous KOH (5.0 ml), and the reaction mixture was heated under reflux for 3 hr. After removal of solvent, the aqueous layer was washed with Et_2O . The aqueous solution was adjusted to pH 2 with 10% aqueous HCl, and extracted with EtOAc. The combined EtOAc extracts were washed with water and brine, dried over Na_2SO_4 , and concentrated. The crude product was purified by SiO_2 column chromatography (EtOAc/MeOH, 20:1) to give the title compound (0.21 g) as violet crystals; mp 110-112 °C;

^1H NMR (CDCl_3): d = 2.45 (3H, s), 4.05 (2H, s), 7.29 (1H, t), 7.37-7.46 (3H, m), 7.53-7.57 (1H, m), 7.56 (1H, t), 7.73-7.75 (2H, m), 8.36 (1H, d), 8.51 (1H, d), 10.63 (1H, bs).

Example 3: (3-Benzoyl-2-methylazulene-1-yl)acetic acid (compound 18)

(a) 1-Acetyl-3-benzoyl-2-methylazulene

To a solution of 1-acetyl-2-methylazulene (5.87 g) in CH_2Cl_2 (80.0 ml) was added AlCl_3 (8.44 g) at 0 °C, and the reaction mixture was stirred for 20 min at same temperature. Then benzoyl chloride

(7.39 ml) was added at same temperature, and the reaction mixture was stirred at room temperature for 1 hr and heated under reflux for 1 hr. The mixture was poured into ice-water, and extracted with Et₂O. The combined Et₂O extracts were washed with water and brine, dried over Na₂SO₄, and concentrated. The residue was crystallized (*n*-hexane/EtOAc) to give the title compound (8.44 g) as violet crystals; mp 122-123 °C;

¹H NMR (CDCl₃):δ = 2.65 (3H, s), 2.74 (3H, s), 7.45-7.57 (3H, m), 7.59 (1H, t), 7.65 (1H, t), 7.78-7.83 (3H, m), 8.50 (1H, d), 9.44 (1H, d).

(b) (3-Benzoyl-2-methylazulene-1-yl)acetic acid (compound 18)

To a solution of 1-acetyl-3-benzoyl-2-methylazulene (0.50 g) in pyridine (3.0 ml) was added sulfur (0.17 g) and morpholine (0.45 g), and the reaction mixture was heated under reflux for 24 hr. The mixture was poured into ice-water, and extracted with EtOAc. The combined EtOAc extracts were washed with 10% aqueous HCl and brine, dried over Na₂SO₄, and concentrated. To the crude product was added 20% aqueous KOH (10.0 ml), and the reaction mixture was heated under reflux for 2 hr. The mixture was washed with Et₂O. The solution was adjusted to pH 2 with 10% aqueous HCl, and extracted with EtOAc. The combined EtOAc extracts were washed with 10% aqueous HCl and brine, dried over Na₂SO₄, and concentrated. The crude product was purified by SiO₂ column chromatography (EtOAc/MeOH, 50:1) to give the title compound (0.069 g) as violet crystals; mp 110-112 °C;

¹H NMR (CDCl₃):δ = 2.45 (3H, s), 4.05 (2H, s), 7.29 (1H, t), 7.37-7.46 (3H, m), 7.53-7.57 (1H, m), 7.65 (1H, t), 7.73-7.75 (2H, m), 8.36 (1H, d), 8.51 (1H, d), 10.63 (1H, bs).

Example 4: (3-Benzyl-2-methylazulene-1-yl)acetic acid (compound 35)

(a) 1-Benzyl-2-methylazulene

To a solution of 3-benzyl-2-methylazulene (0.58 g) in Et₂O (10.0 ml)/diglyme (20.0 ml) was added BF₃-Et₂O complex (1.76 ml) and sodium cyanoborohydride (0.88 g) at 0 °C, and the reaction mixture was heated under reflux for 9 hr. The mixture was poured into 10% aqueous HCl, and extracted with Et₂O. The combined Et₂O extracts were washed with water, saturated aqueous NaHCO₃ and brine, dried over Na₂SO₄, and concentrated. The crude product was purified by SiO₂ column chromatography (Et₂O/*n*-hexane, 1:5) to give the title compound (0.50 g) as violet crystals; mp 67-68 °C;

¹H NMR (CDCl₃):δ = 2.51 (3H, s), 4.40 (2H, s), 7.04-7.13 (5H, m), 7.18-7.22 (3H, m), 7.45 (1H, t), 8.15 (1H, d), 8.16 (1H, d).

(b) 1-(3-Benzyl-2-methyl)methylazulenetrtrimethylammonium iodide A mixture of paraformaldehyde

(0.05 g), *N,N,N',N'*-tetramethyldiaminomethane (0.25 g) and acetic acid (4.6 ml) was heated and stirred at 80 °C for 20 min. Then a solution of 1-benzyl-2-methylazulene (0.51 g) in CH₂Cl₂ (18.0 ml) was added at 0 °C, and the reaction mixture was stirred at room temperature for 1 hr. The reaction mixture was adjusted to pH 10 with 10% aqueous NaOH, and extracted with CH₂Cl₂. The combined CH₂Cl₂ extracts were washed with water and brine, dried over Na₂SO₄, and concentrated. Methyl iodide (5.0 ml) was added to the solution of the crude product in EtOH (10.0 ml), and the reaction mixture was stirred at room temperature for 2 hr. Then the crystals were collected by filtration to give the title compound (0.90 g) as violet crystals; mp 174-175 °C;

¹H NMR (CDCl₃):δ = 2.58 (3H, s), 3.04 (9H, s), 4.44 (2H, s), 4.90-5.08 (2H, m), 7.08 (2H, d), 7.13 (1H, t), 7.22 (1H, t), 7.38 (1H, t), 7.42 (1H, t), 7.76 (1H, t), 8.50 (1H, d), 9.67 (1H, d).

(c) 3-Benzyl-2-methyl-1-cyanomethylazulene

To a suspension of 1-(3-benzyl-2-methyl)methylazulenetrtrimethylammonium iodide (0.85 g) in EtOH (10.0 ml) was added KCN (0.26 g), and the reaction mixture was heated under reflux for 2 hr. The reaction mixture was poured into water, and extracted with Et₂O. The combined Et₂O extracts were washed with water and brine, dried over Na₂SO₄, and concentrated. The crude product was purified by SiO₂ column chromatography (Et₂O/n-hexane, 3:4) to give the title compound (0.47 g) as violet crystals; mp 93-94 °C;

¹H NMR (CDCl₃):δ = 2.53 (3H, s), 4.09 (2H, s), 4.42 (2H, s), 7.05 (2H, d), 7.13-7.24 (5H, m), 7.56 (1H, t), 8.17 (1H, d), 8.24 (1H, d).

(d) (3-Benzyl-2-methylazulene-1-yl)acetic acid (compound 35)

To a suspension of 3-benzyl-2-methyl-1-cyanomethylazulene (0.44 g) in EtOH (10.0 ml) was added 20% aqueous KOH (5.0 ml), and the reaction mixture was heated under reflux for 3 hr. After removal of solvent, the aqueous layer was washed with Et₂O. The aqueous solution was adjusted to pH 2 with 10% aqueous HCl, and extracted with EtOAc. The combined EtOAc extracts were washed with water and brine, dried over Na₂SO₄, and concentrated. The crude product was purified by SiO₂ column chromatography (EtOAc/n-hexane, 3:1) to give the title compound (0.27 g) as violet crystals; mp 142-143 °C;

¹H NMR (CDCl₃):δ = 2.48 (3H, s), 4.07 (2H, s), 4.41 (2H, s), 7.04-7.22 (7H, m), 7.48 (1H, t), 8.18 (1H, d), 8.19 (1H, d), 10.98 (1H, bs).

Example 5: 3-(3-benzoyl-2-methyl-1-yl)propionic acid (compound 38)

(a) Dimethyl 2-(3-benzoyl-2-methylazulene-1-yl)ethylmalonate

To a suspension of sodium hydride (0.54 g) in THF (30.0 ml) was added a solution of dimethyl malonate (1.78 g) in THF (10.0 ml) at 0 °C, and the reaction mixture was stirred for 15 min. Then

HMPA (40.0 ml) and 1-(3-benzoyl-2-methyl)methylazulenetrtrimethylammonium iodide (2.0 g) was added, the reaction mixture was stirred for 30 min. The reaction mixture was added to a saturated aqueous NH₄Cl, and extracted with Et₂O. The combined Et₂O extracts were washed with water and brine, dried over Na₂SO₄, and concentrated. The crude product was purified by SiO₂ column chromatography (EtOAc/MeOH, 1:2) to give the title compound (1.42 g) as violet crystals; mp 63-64 °C;
¹H NMR (CDCl₃): δ = 2.43 (3H, s), 3.66 (6H, s), 3.67-3.76 (3H, m), 7.26 (1H, t), 7.35 (1H, t), 7.43-7.46 (2H, m), 7.54-7.61 (1H, m), 7.66 (1H, t), 7.71-7.73 (2H, m), 8.39 (1H, d), 8.47 (1H, d).

(b) 3-(3-Benzoyl-2-methylazulene-1-yl)propionic acid (compound 38)

To a suspension of dimethyl 2-(3-benzoyl-2-methylazulene-1-yl)ethylmalonate (1.2 g) in MeOH (20.0 ml) was added 10% aqueous NaOH (20.0 ml), and the reaction mixture was heated under reflux for 2 hr. After removal of solvent, the aqueous layer was washed with Et₂O. The aqueous solution was adjusted to pH 2 with 10% aqueous HCl, and extracted with EtOAc. The combined EtOAc extracts were washed with water and brine, dried over Na₂SO₄, and concentrated. The obtainable crude product was suspended with toluene (50.0 ml), and then this suspension was heated under reflux for 24 hr. The reaction mixture was concentrated. The crude product was purified by SiO₂ column chromatography (EtOAc/n-hexane, 3:1) to give the title compound (0.73 g) as violet crystals; mp 140-141 °C;

¹H NMR (CDCl₃): δ = 2.45 (3H, s), 2.67 (2H, t), 3.38 (2H, t), 7.23-7.27 (1H, m), 7.38 (1H, t), 7.43-7.47 (2H, m), 7.62 (1H, t), 7.53-7.64 (1H, m), 7.73-7.75 (2H, m), 8.36 (1H, d), 8.46 (1H, d), 10.46 (1H, bs).

Example 6: 3-(3-Benzyl-2-methylazulene-1-yl)propionic acid (compound 56)

(a) Dimethyl 3-(3-benzyl-2-methylazulene-1-yl)ethylmalonate

To a suspension of sodium hydride (0.31 g) in THF (20.0 ml) was added a solution of dimethyl malonate (1.04 g) in THF (10.0 ml) at 0 °C, and the reaction mixture was stirred for 15 min. Then HMPA (20.0 ml) and 1-(3-benzyl-2-methyl)methylazulenetrtrimethylammonium iodide (1.13 g) was added, the reaction mixture was heated under reflux for 1 hr. The reaction mixture was added to a saturated aqueous NH₄Cl, and extracted with Et₂O. The combined Et₂O extracts were washed with water and brine, dried over Na₂SO₄, and concentrated. The crude product was purified by SiO₂ column chromatography (Et₂O/MeOH, 1:2) to give the title compound (0.99 g) as violet crystals; mp 87-88 °C;

¹H NMR (CDCl₃): δ = 2.44 (3H, s), 3.61 (6H, s), 3.71-3.81 (3H, m), 4.40 (2H, s), 7.26 (1H, t), 7.00-7.21 (7H, m), 7.46 (1H, t), 8.13 (1H, d), 8.19 (1H, d).

(b) 3-(3-Benzyl-2-methylazulene-1-yl)propionic acid (compound 56)

To a suspension of dimethyl 2-(3-benzyl-2-methylazulene-1-yl)ethylmalonate (0.99 g) in MeOH (20.0 ml) was added 10% aqueous NaOH (10.0 ml), and the reaction mixture was heated under reflux for 2 hr. After removal of solvent, the aqueous layer was washed with Et₂O. The aqueous solution was adjusted to pH 2 with 10% aqueous HCl, and extracted with EtOAc. The combined EtOAc extracts were washed with water and brine, dried over Na₂SO₄, and concentrated. The obtainable crude product was suspended with toluene (30.0 ml), and then this suspension was heated under reflux for 24 hr. The reaction mixture was concentrated. The crude product was purified by SiO₂ column chromatography (EtOAc/n-hexane, 3:1) to give the title compound (0.60 g) as violet crystals; mp 161-162 °C;

¹H NMR (CDCl₃):δ = 2.47 (3H, s), 2.64 (2H, t), 3.40 (2H, t), 4.42 (2H, s), 7.00-7.14 (5H, m), 7.20 (1H, t), 7.46 (1H, t), 8.18 (1H, d), 8.14 (1H, d), 11.06 (1H, bs).

Example 7: Ethyl (3-benzoyl-2-methylazulene-1-yl)acetate (compound 66)

To a solution of (3-benzoyl-2-methylazulene-1-yl)acetic acid (0.40 g) in *N,N*-dimethylacetamide (20.0 ml) was added NaHCO₃ (0.33 g), and ethyl iodide (0.3 ml), and the reaction mixture was stirred for 16 hr. The mixture was poured into ice-water, followed by extraction with EtOAc. The combined EtOAc extracts were washed with water and brine, dried over Na₂SO₄, and concentrated. The crude product was purified by SiO₂ column chromatography (EtOAc/n-hexane, 1:2) to give the title compound (0.35 g) as violet crystals; mp 65-66 °C;

¹H NMR (CDCl₃):δ = 1.23 (3H, t), 2.46 (3H, s), 4.03 (2H, s), 4.13 (2H, q), 7.29 (1H, t), 7.38-7.47 (3H, m), 7.56 (1H, t), 7.65 (1H, t), 7.76 (2H, d), 8.41 (1H, d), 8.53 (1H, d).

Example 8: (5-Methyl-2-oxo-1,3dioxol-4-yl)methyl (3-benzoyl-2-methylazulene-1-yl)acetate (compound 71)

To a solution of (3-benzyl-2-methylazulene-1-yl)acetic acid (0.40 g) in *N,N*-dimethylacetamide (10.0 ml) was added NaHCO₃ (0.17 g), and 4-(chloromethyl)-5-methyl-1,3-dioxol-2-one (0.29 g), and the reaction mixture was stirred at 50 °C for 3hr. The mixture was poured into ice-water, followed by extraction with EtOAc. The combined EtOAc extracts were washed with water and brine, dried over Na₂SO₄, and concentrated. The crude product was purified by SiO₂ column chromatography (EtOAc/n-hexane, 3:4) to give the title compound (0.40 g) as violet crystals; mp 121-123 °C;

¹H NMR (CDCl₃):δ = 2.11 (3H, s), 2.95 (3H, s), 4.09 (2H, s), 4.83 (2H, s), 7.32 (1H, t), 7.43 (1H, t), 7.40-7.48 (2H, m), 7.56 (1H, t), 7.68 (1H, t), 7.68-7.76 (2H, m), 8.36 (1H, d), 8.53 (1H, d).

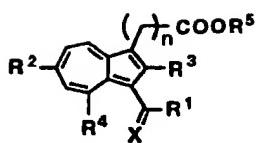
Melting points of compounds 1-75 were listed in Table 2 and 3.

[Table 2]



Compounds	R¹	R²	R³	R⁴	R⁵	X	n	Melting point (°C)
1	phenyl	H	Me	H	H	O	0	198-199
2	phenyl	i-Pr	Me	H	H	O	0	171-173
3	2-chlorophenyl	H	Me	H	H	O	0	218-220
4	3-chlorophenyl	H	Me	H	H	O	0	209-210
5	4-chlorophenyl	H	Me	H	H	O	0	217-218
6	4-chlorophenyl	i-Pr	Me	H	H	O	0	196-198
7	3-bromophenyl	H	Me	H	H	O	0	207-208
8	4-bromophenyl	H	Me	H	H	O	0	215-216
9	4-bromophenyl	i-Pr	Me	H	H	O	0	198-200
10	3-methylphenyl	H	Me	H	H	O	0	206-207
11	4-methylphenyl	H	Me	H	H	O	0	214-215
12	4-methoxyphenyl	H	Me	H	H	O	0	204-205
13	4-trifluorophenyl	H	Me	H	H	O	0	219-220
14	3-chloro-4-methoxyphenyl	H	Me	H	H	O	0	201-203
15	3,5-dichlorophenyl	H	Me	H	H	O	0	241-243
— 16	2-furyl	H	Me	H	H	O	0	214-215
— 17	2-thienyl	H	Me	H	H	O	0	191-192
18	phenyl	H	Me	H	H	O	1	110-112
19	phenyl	i-Pr	Me	H	H	O	1	177-179
20	2-chlorophenyl	H	Me	H	H	O	1	162-163
21	3-chlorophenyl	H	Me	H	H	O	1	137-138
22	4-chlorophenyl	H	Me	H	H	O	1	216-218
23	4-chlorophenyl	i-Pr	Me	H	H	O	1	160-162
24	3-bromophenyl	H	Me	H	H	O	1	138-140
25	4-bromophenyl	H	Me	H	H	O	1	227-228
26	4-bromophenyl	i-Pr	Me	H	H	O	1	173-175
27	3-methylphenyl	H	Me	H	H	O	1	138-139
28	4-methylphenyl	H	Me	H	H	O	1	131-133
29	4-methoxyphenyl	H	Me	H	H	O	1	143-144
30	4-trifluorophenyl	H	Me	H	H	O	1	186-187
31	3-chloro-4-methoxyphenyl	H	Me	H	H	O	1	193-195
32	3,5-dichlorophenyl	H	Me	H	H	O	1	194-195
— 33	2-furyl	H	Me	H	H	O	1	141-142
— 34	2-thienyl	H	Me	H	H	O	1	144-145
35	phenyl	H	Me	H	H	H ₂	1	142-143
36	phenyl	i-Pr	Me	H	H	H ₂	1	133-134
37	4-chlorophenyl	H	Me	H	H	H ₂	1	156-157
38	phenyl	H	Me	H	H	O	2	140-141

[Table 3]



Compounds	R ¹	R ²	R ³	R ⁴	R ⁵	X	n	Melting point (°C)
39	phenyl	i-Pr	Me	H	H	O	2	155-157
40	2-chlorophenyl	H	Me	H	H	O	2	162-163
41	2-chlorophenyl	i-Pr	Me	H	H	O	2	144-145
42	3-chlorophenyl	H	Me	H	H	O	2	205-206
43	4-chlorophenyl	i-Pr	Me	H	H	O	2	155-157
44	4-chlorophenyl	H	Me	H	H	O	2	201-203
45	3-bromophenyl	H	Me	H	H	O	2	122-123
46	4-bromophenyl	H	Me	H	H	O	2	212-213
47	4-bromophenyl	i-Pr	Me	H	H	O	2	170-172
48	3-methylphenyl	H	Me	H	H	O	2	147-148
49	4-methylphenyl	H	Me	H	H	O	2	117-118
50	4-methoxyphenyl	H	Me	H	H	O	2	133-135
51	4-trifluorophenyl	H	Me	H	H	O	2	162-163
52	3-chloro-4-methoxyphenyl	H	Me	H	H	O	2	182-183
53	3,5-dichlorophenyl	H	Me	H	H	O	2	186-187
- 54	2-furyl	H	Me	H	H	O	2	153-154
- 55	2-thienyl	H	Me	H	H	O	2	163-165
56	phenyl	H	Me	H	H	H ₂	2	161-162
57	4-chlorophenyl	H	H	H	H	H ₂	2	183-184
58	phenyl	H	H	H	H	O	0	210-212
59	phenyl	H	Et	H	H	O	1	168-169
60	phenyl	H	Et	H	H	O	0	188-189
61	phenyl	H	i-Pr	H	H	O	1	167-168
62	phenyl	H	i-Pr	H	H	O	0	165-166
63	phenyl	H	Me	H	H	O	1	133-135
64	phenyl	H	Me	OMe	H	O	0	195-196
65	phenyl	H	Me	OMe	H	O	1	182-183
66	phenyl	H	Me	H	Et	O	1	65-66
67	2-chlorophenyl	H	Me	H	Et	O	1	72-73
68	4-methylphenyl	H	Me	H	Et	O	1	62-63
69	4-bromophenyl	H	Me	H	Et	O	1	111-113
- 70	2-thienyl	H	Me	H	Et	O	1	53-55
71	phenyl	H	Me	H	A	O	1	121-123
- 72	2-chlorophenyl	H	Me	H	A	O	1	114-116
- 73	4-methylphenyl	H	Me	H	A	O	1	68-69
- 74	4-bromophenyl	H	Me	H	A	O	1	86-87
- 75	2-thienyl	H	Me	H	A	O	1	92-93

A is a (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl group.

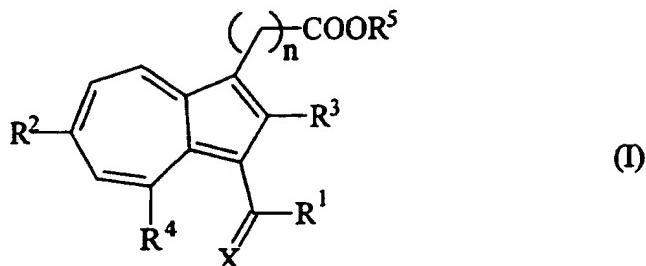
EFFECTIVENESS OF THE INVENTION

The compounds of general formula (I) or the salt thereof are selective COX-2 inhibitors having excellent antiinflammatory, analgesic, antipyretic and antiarthritis activities and useful as antiinflammatory agents without side effects such as gastrointestinal irritation.

CLAIMS

1. A compound which is an azulene derivative of formula (I):

5



10

wherein R¹ is a substituted or unsubstituted benzene ring or a heteroaromatic ring, R² is hydrogen or lower alkyl, R³ is hydrogen or lower alkyl, R⁴ is hydrogen or lower alkoxy, R⁵ is hydrogen, lower alkyl or (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl, X is hydrogen or oxygen and n is 0, 1 or 2; or a pharmaceutically acceptable alkali addition salt thereof.

2. A compound according to claim 1 wherein, in formula (I), R¹ is a benzene, furan or thiophene ring which is unsubstituted or substituted by one or two substituents selected from methyl, trifluoromethyl, methoxy, chlorine and bromine, R² is hydrogen or isopropyl, R³ is hydrogen, methyl, ethyl or isopropyl, R⁴ is hydrogen or methoxy, R⁵ is hydrogen, ethyl or (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl, X is hydrogen or oxygen and n is 0.

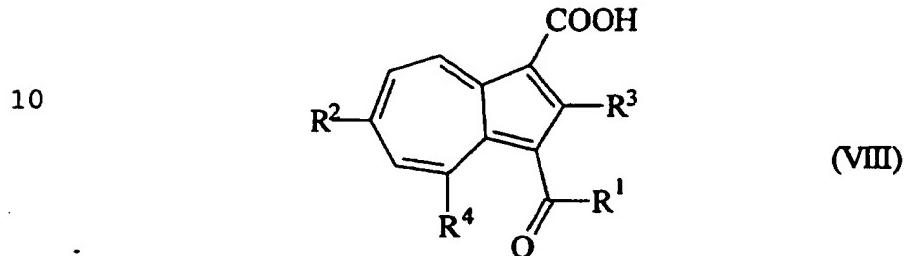
3. A compound according to claim 1 wherein, in formula (I), R¹ is a benzene, furan or thiophene ring which is unsubstituted or substituted by one or two substituents selected from methyl, trifluoromethyl, methoxy, chlorine and bromine, R² is hydrogen or isopropyl, R³ is hydrogen, methyl, ethyl, or isopropyl, R⁴ is hydrogen or methoxy, R⁵ is hydrogen, ethyl or (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl, X is hydrogen or oxygen and n is 1.

30

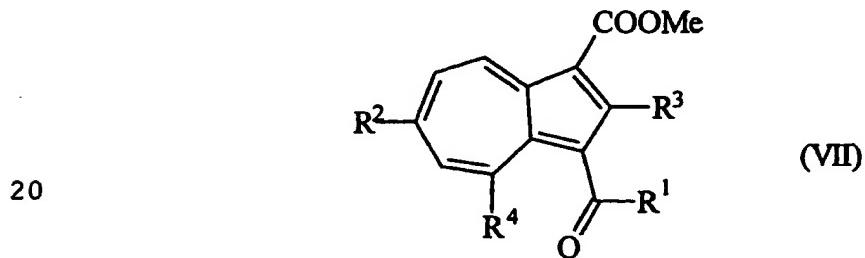
4. A compound according to claim 1 wherein, in formula (I), R¹ is a benzene,

furan or thiophene ring which is unsubstituted or substituted by one or two substituents selected from methyl, trifluoromethyl, methoxy, chlorine and bromine,
R² is hydrogen or isopropyl, R³ is hydrogen, methyl, ethyl or isopropyl, R⁴ is
hydrogen or methoxy, R⁵ is hydrogen, ethyl or (5-methyl-2-oxo-1,3-dioxol-4-
5 yl)methyl, X is hydrogen or oxygen and n is 2.

5. A process for producing a compound of formula (VIII):

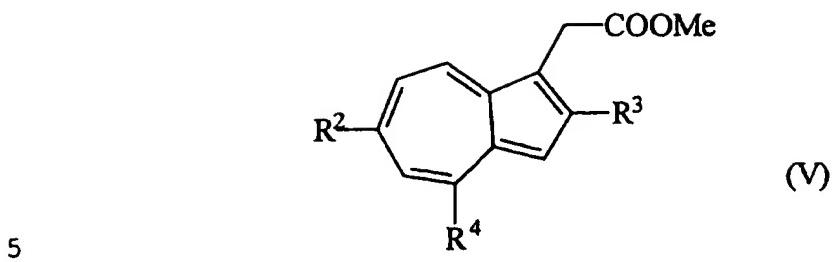


wherein R¹, R², R³ and R⁴ are as defined in claim 1, which process comprises
15 hydrolysing a compound of formula (VII):



wherein R¹, R², R³ and R⁴ are as defined in claim 1.

25 6. A process according to claim 5 which comprises the further step of
producing the compound of formula (VII) by reacting a compound of general
formula (V):



wherein: R¹, R², R³ and R⁴ are as defined in claim 1 with a compound of general formula (VI):

10

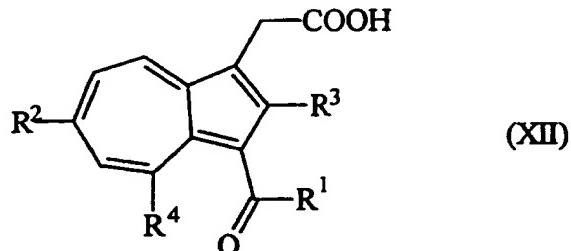


wherein R¹, R², R³ and R⁴ are as defined in claim 1.

15

7. A process for producing a compound of formula (XII):

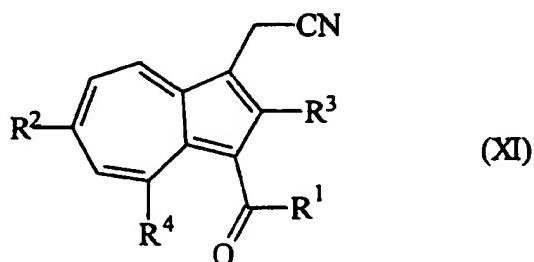
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wherein R¹, R², R³ and R⁴ are as defined in claim 1, which process comprises hydrolysing a compound of formula (XI):

25

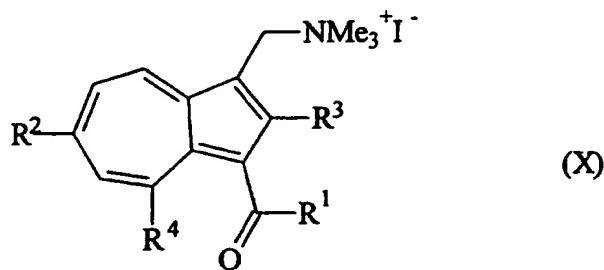
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wherein R¹, R², R³, and R⁴ are as defined in claim 1.

8. A process according to claim 7 which comprises the further step of
producing the compound of formula (XI) by submitting to cyanation a compound of
5 formula (X):

10

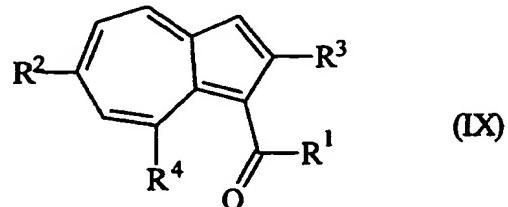


wherein R¹, R², R³ are as defined in claim 1.

15

9. A process according to claim 8 which comprises the further step of
producing the compound of formula (X) by submitting a compound of formula
(IX):

20



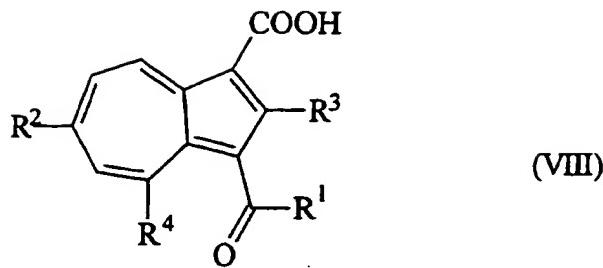
25

wherein R¹, R², R³ and R⁴ are as defined in claim 1 to a Mannich reaction and
quaternisation.

10. A process according to claim 9 which comprises the further step of
producing the compound of formula (IX) by decarbonylating a carboxylic acid of
general formula (VIII):

30

5

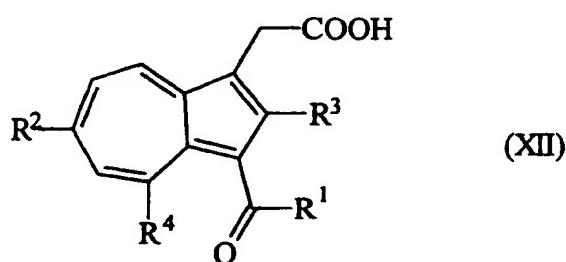


(VIII)

wherein R^1 , R^2 , R^3 and R^4 are as defined in claim 1.

10

15

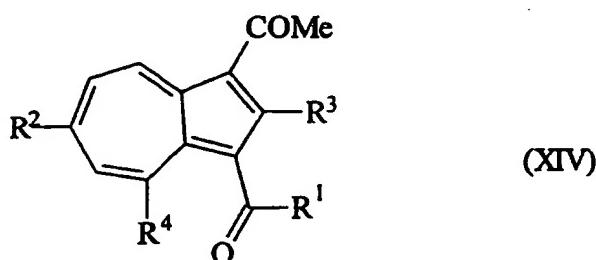


(XII)

wherein R^1 , R^2 , R^3 and R^4 are as defined in claim 1, which process comprises converting a compound of formula (XIV):

20

25



(XIV)

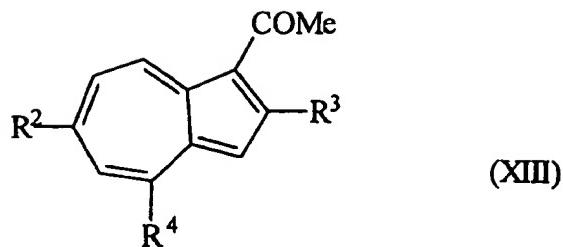
wherein R^1 , R^2 , R^3 and R^4 are as defined in claim 1, to the corresponding thiomorpholide by the Willgerodt-kindler reaction and then hydrolysing the thiomorpholide.

30

12. A process according to claim 11 which comprises the further step of producing the compound of formula (XIV) by reacting a compound of formula

(XIII):

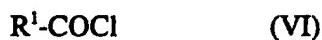
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(XIII)

wherein R¹, R², R³ and R⁴ are as defined in claim 1, with a compound of general formula (VI):

10

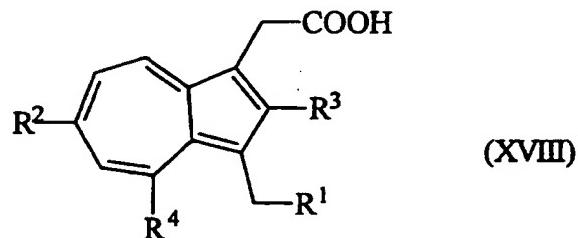


wherein R¹, R², R³ and R⁴ are as defined in claim 1.

15

13. A process for producing a compound of formula (XVIII):

20

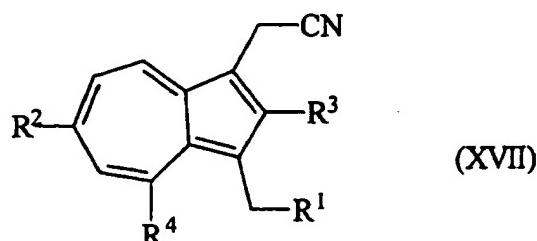


(XVIII)

wherein R¹, R², R³ and R⁴ are as defined in claim 1, which method comprises hydrolysing a compound of formula (XVII):

25

30

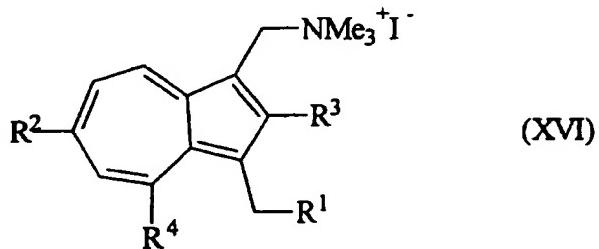


(XVII)

wherein R¹, R², R³ and R⁴ are as defined in claim 1.

14. A process according to claim 13 which comprises the further step of
producing the compound of formula (XVII) by submitting to cyanation a compound
5 of formula (XVI):

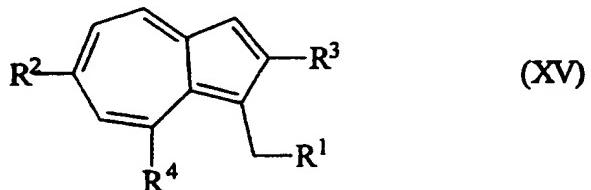
10



wherein R¹, R², R³ and R⁴ are as defined in claim 1.

15 15. A process according to claim 14 which comprises the further step of
producing the compound of formula (XVI) by submitting a compound of formula
20 (XV):

20

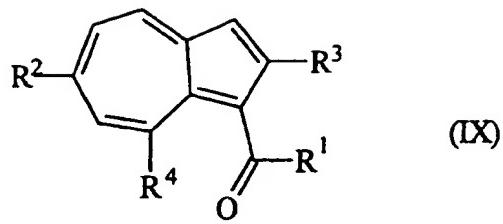


wherein R¹, R², R³, and R⁴ are as defined in claim 1 to a Mannich reaction and

25 quaternisation.

16. A process according to claim 15 which comprises the further step of
producing the compound of formula (XV) by reducing a compound of formula
30 (IX):

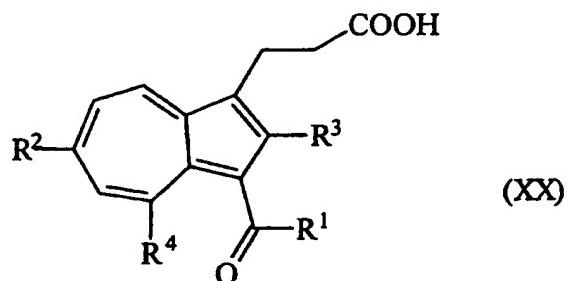
30



wherein R¹, R², R³ and R⁴ are as defined in claim 1.

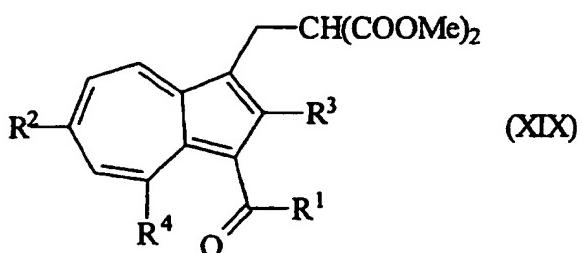
10 17. A process for producing a compound of formula (XX):

10



wherein R¹, R², R³ and R⁴ are as defined in claim 1, which process comprises hydrolysing and decarbonylating a compound of formula (XIX):

20

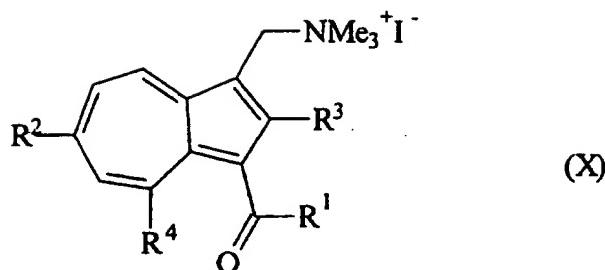


25

wherein R¹, R², R³ and R⁴ are as defined in claim 1.

30 18. A process according to claim 17 which comprises the further step of producing the compound of formula (XIX) by reacting a compound of formula (X):

5

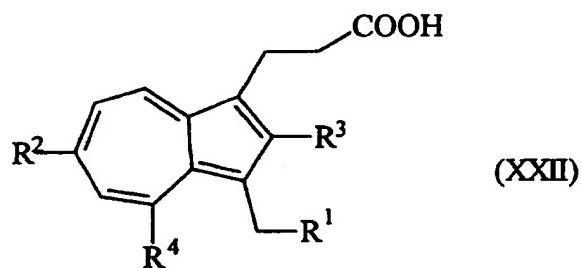


wherein R¹, R², R³ and R⁴ are as defined in claim 1, with malonic acid ester.

10

19. A process for producing a compound of formula (XXII):

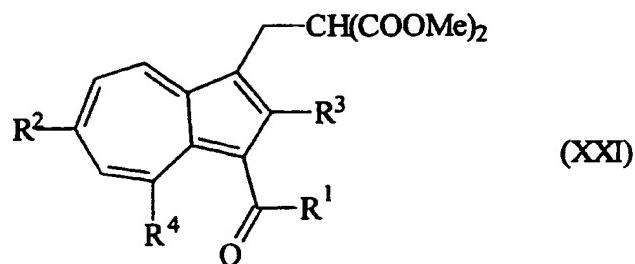
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20

wherein R¹, R², R³ and R⁴ are as defined in claim 1, which process comprises hydrolysing and decarbonylating a compound of formula (XXI):

25



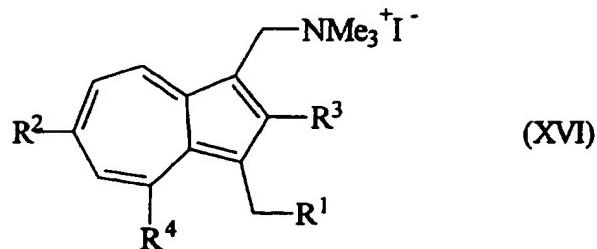
wherein R¹, R², R³ and R⁴ are as defined in claim 1.

30

20. A process according to claim 19 which comprises the further step of

producing the compound of formula (XXI) by reacting a compound of formula (XVI):

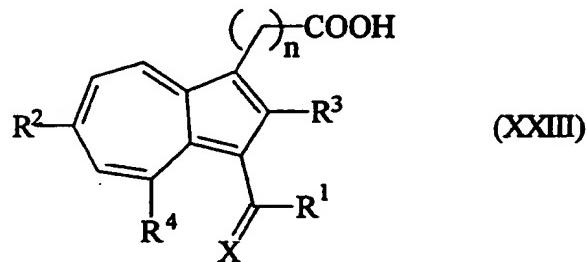
5



10 wherein R¹, R², R³ and R⁴ are as defined in claim 1, with malonic acid ester.

21. A process for producing a compound as defined in claim 1, which process comprises alkylating a compound of formula (XXIII):

15



20

wherein X, R¹, R², R³, and R⁴ are as defined in claim 1, with a compound of formula (XXIV):



25 wherein R⁵ is lower alkyl or (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl and Y is a halogen.

30 22. A process according to any one of claims 5 to 21 which comprises the further step of converting the resulting azulene derivative into a pharmaceutically acceptable alkali addition salt thereof.

23. A process according to any one of claims 5 to 22, substantially as hereinbefore described in any one of the Examples.

24. A compound produced by a process as defined in any one of claims 5 to 23.

5

25. A compound as defined in claim 1, specifically hereinbefore mentioned.

10

26. A pharmaceutical composition comprising a pharmaceutically acceptable carrier or diluent and, as an active ingredient, a compound as defined in any one of claims 1 to 4, 24 and 25.

27. A compound as defined in any one of claims 1 to 4, 24 and 25 for use in a method of treatment of the human or animal body by therapy or prophylaxis.

15

28. A compound as claimed in claim 27 for use as an inhibitor of cyclooxygenase-2.

29. A compound according to claim 28 for use in the treatment of inflammation, pain, fever or arthritis.

20

30. Use of a compound as defined in any one of claims 1 to 4 in the manufacture of a medicament for use in the treatment of inflammation, pain, fever or arthritis.

25